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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61M 1/00 — A1

(11) International Publication Number: WO 95/20983

(43) International Publication Date: 10 August 1995 (10.08.95)

(21) International Application Number: PCT/SE95/00095

(22) International Filing Date: 1 February 1995 (01.02.95)

(30) Priority Data:
9400377-9 4 February 1994 (04.02.94) SE

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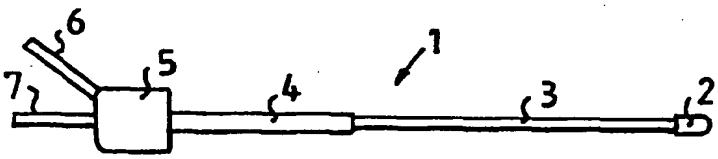
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
In English translation (filed in Swedish).

(54) Title: REINFORCED MICRODIALYSIS PROBE

(57) Abstract

The invention relates to a microdialysis probe of the kind in which a centre tube is surrounded by a thin dialysis tube (3), which is located between two tubular fitting parts (2, 5). With the purpose of reinforcing the probe and facilitating its withdrawal without any part of the probe remaining despite the fragility of the dialysis tube, the distal end of the centre tube is, according to the invention, from within is fixedly joined to the distal fitting part (2), which also has a larger diameter than the dialysis tube (3).



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REINFORCED MICRODIALYSIS PROBE

The invention relates to a microdialysis probe of the kind defined in the preamble of the following Claim 1. A dialysis probe of this kind is described in SE-C-434 214.

By microdialysis is meant a method of examination in which a probe is inserted into tissue in vivo, such that one side of a semi-permeable membrane is in contact with tissue and body fluid, while the other side is flushed or rinsed with a dialysis liquid which takes-up substances through the membrane, which substances can then be analyzed in the liquid that has flown past. This method has made large advances in recent years and the number of research publications relating to microdialysis have multiplied in frequency a thousand-fold in ten years.

The use in clinical and polyclinical activities for diagnostic purposes on human beings, however, has been held back, primarily because dialysis probes are relatively fragile by nature, which makes it difficult to insert and remove the probe. At least part of the probe must have a surface which consists of a thin, semi-permeable membrane which is easily broken, particularly when removing the probe. The problem is not as large during insertion, since during insertion an external tube is normally used which is removed after insertion while leaving the probe in place. This outer tube may have the form of a plastic tube which can be withdrawn and slit flush with the skin as the tube is gradually withdrawn, with the probe left in position.

However, when the probe is inserted into tissue of a living person, the probe must be able to retain its shape despite the stresses and strains that can be expected when the person moves. A still greater problem occurs when the probe is to be withdrawn after use. In the case of the known probe, withdrawal may result in part of it being left in the body.

Accordingly, it is an object of the invention to provide a microdialysis probe which is suitable for general human use when taking samples for a diagnostic purpose as a routine method. In particular the risk of material being left behind when the probe is withdrawn must be overcome.

These and other objects are achieved and the aforementioned risks avoided to the highest degree in accordance with the invention by modifying a microdialysis probe of the kind defined in the introduction in the manner defined in the characterizing clause of the following Claim 1. Preferred embodiments are defined in the depending Claims.

Because the distal end of the probe is fixedly joined to the centre tube, safe withdrawal of this end is guaranteed. Furthermore, it is also ensured that no part of the mantle tube will remain, since even if the tube should be broken, the worst that can happen is only a certain degree of movement towards the distal end, which has a larger diameter and which when withdrawn from the insertion hole will entrain any pieces that may have broken off from the mantle tube.

The invention will now be described in more detail with reference to an illustrative but not limiting embodiment thereof. Fig. 1 is a schematic side view of a microdialysis probe. Fig. 2 illustrates a centre tube. Fig. 3 illustrates in larger scale and in section a distal end of a microdialysis probe. Fig. 4 shows a proximal end of a microdialysis probe also in larger scale and in section.

The probe 1 shown in Fig. 1 has at its distal end an enlarged fitting in the form of a first tube 2 from which there protrudes a mantle tube 3, which is somewhat narrower. The mantle tube 3 extends to a second tube 4 and penetrates said tube. In turn, the second tube 4 extends to a distal end-piece 5, from which two external connecting pipes 6 and 7 extend.

In accordance with the invention, it is not actually the at least partially very thin mantle tube 3 which is the supporting structure, but that the mantle tube encases a centre tube 8 which extends between the end-piece 5 and the fitting 2 and which is fastened to the fitting 2 so that the mantle tube 3 is essentially clamped between the fitting 2 and the distal end of the tube 4. The centre tube is shown in Fig. 2, and is closed and enlarged at its distal end. As will be seen from Fig. 3, the centre tube is taken up in the fitting 2, where it is accommodated, surrounded by a glue, preferably at least partially by shape conformity. If the tube 8 is made of plastic, the end of the tube is appropriately formed by melting.

As will be seen from Fig. 4, the centre tube 8 is connected in the end-piece 5 to one of the pipes 6 and 7, whereas the other of said pipes discharges into the space between the centre tube 8 and the second tube 4. To facilitate symmetric and problem-free withdrawal, the centre tube extends perfectly straight, from the end-piece 5 which is never inserted into the body, up to the thickening 9 at the distal end. Even should the membrane break in the actual passage through the skin - human skin can be relatively tough and elastic - the membrane will be withdrawn seated on the enlarged end at the distal end of the centre tube.

EXAMPLE

A tube of hard polyurethane having an outer diameter of 0.4 mm and an inner diameter of 0.12 mm was fused together at one end, so as to obtain an approximately hemispherical ball 9 having a diameter of 0.6 mm. Two opposing holes having a diameter of 0.1 mm were made at an axial distance of about 0.5 mm therefrom. This resulted in a centre tube according to Fig. 2 having the measurements disclosed in the Figure. An outer part was manufactured by threading a membrane 3 of polyamide of the same type as that used in artificial kidneys and having

a thickness of 50 µm and a diameter of 0.5 mm onto a mandrel. Hoses 2 and 4 having an internal diameter of 0.65 mm were applied from both sides and the ends of the hoses were glued firmly to the membrane with polyurethane glue. The whole was withdrawn from the mandrel and the centre tube was fitted from the distal side, thus with the ball 9 last, whereafter glue was injected between the tube 2 and the ball 9, in accordance with what is shown in Fig. 3. A hose 7 was secured to the other end of the centre tube, and another hose 6 was mounted with connection to the interspace between the tubes 4 and 8, the whole being surrounded by a moulded plastic 5.

In order to insert such a catheter some form of stiffening is required, for instance a surrounding cannula which can be removed after insertion. There are available steel cannula that are provided with two longitudinally extending weakenings which enable the cannula to be withdrawn and split into two halves so that it can be removed.

"Dialysis liquid" can now be pressed in through one of the connecting pipes 6, 7 in a known manner, and after taking up the substances through the semi-permeable mantle tube is collected from the other connecting pipe. It is preferred to use as the introduction pipe the pipe which is in direct communication with the space between the membrane tube and the centre tube, in view of the fact that the "dead space" is thereby minimised. The outcoming liquid volume is then subjected to conventional microanalysis, which forms no part of the present invention.

CLAIMS

1. A microdialysis probe having two external connecting pipes (6, 7), a centre tube (8) surrounded by a semi-permeable mantle tube (3), wherein the centre tube has a distal opening (10, 11) and is connected at its proximal end to either one of the external connecting pipes (7) and the space formed at its proximal end (5) between the centre tube (8) and the mantle tube (8) is connected to the other of said two external connecting pipes (6), and the mantle tube (3) is partially surrounded by a fitting (2, 4) which supports and partially exposes the mantle tube, **characterized** in that the fitting includes a first tube (4) which is fastened to the proximal end of the mantle tube and surrounds said proximal end thereof, and a second tube (2) which is fastened to the mantle tube and surrounds the distal end thereof and which is closed at said distal end, wherein the centre tube (8) includes at its distal end an enlargement (9) which is accommodated, preferably with shape conformity, within the second tube, and wherein the distal opening of the centre tube is located in a side surface thereof and opens into the space formed between the centre tube and the mantle tube.

2. A microdialysis probe according to Claim 1, **characterized** in that the tubes (2, 4) belonging to the fitting are made of plastic.

3. A microdialysis probe according to Claim 1 or 2, **characterized** by glue which is laid between the distal enlargement (9) of the centre tube (8) and the distal end of the second tube (2) and which forms an attachment to the centre tube and a closure at the distal end of the second tube.

4. A microdialysis probe according to any one of the preceding Claims, **characterized** in that the second tube (2) forms an enlargement of the distal end of the probe (1), this enlargement having a larger outer diameter than the outer

diameter of the mantle tube (3).

5. A microdialysis probe according to any one of the preceding Claims, characterized in that the mantle tube has a wall thickness of 15-50 µm.

6. A microdialysis probe according to Claim 5, characterized in that the mantle tube is made of polyamide or cellulose.

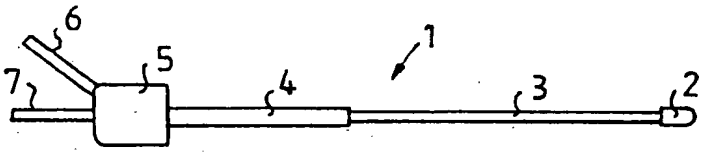

FIG.1

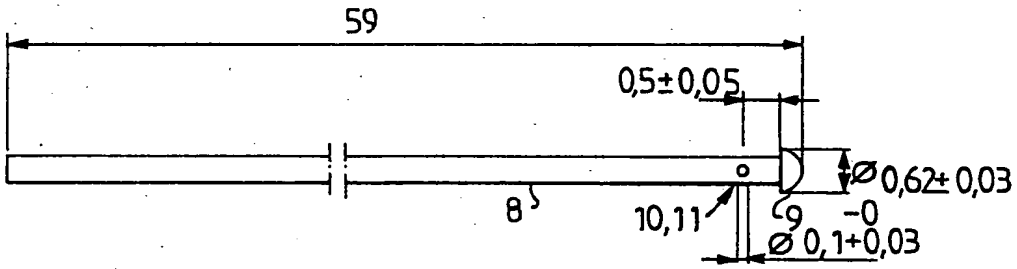

FIG. 2

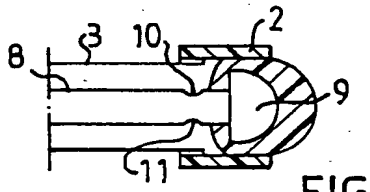

FIG. 3

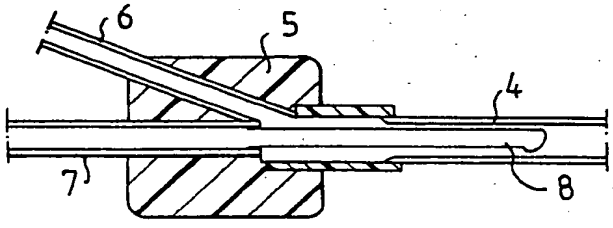

FIG.4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00095

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61M 1/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61M, A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0401179 (AMPLISCIENTIFICA SRL), 5 December 1990 (05.12.90), page 3, line 43 - page 4, line 21, figure 4 --	1-6
A	EP, A1, 0403394 (EUROPHOR, SOCIETE ANONYME), 19 December 1990 (19.12.90) --	1-6
A	DE, C2, 3342170 (UNGERSTEDT, CARL URBAN), 23 January 1992 (23.01.92) -- --------	1-6

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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15 May 1995	30 -05- 1995
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0401179	05/12/90	US-A- 5176632	05/01/93
		US-A- 5298022	29/03/94
EP-A1- 0403394	19/12/90	FR-A,B- 2648353	21/12/90
		US-A- 5106365	21/04/92
DE-C2- 3342170	23/01/92	AT-B- 396871	27/12/93
		AU-B- 568104	17/12/87
		AU-A- 2175983	07/06/84
		BE-A,A- 898342	30/05/84
		CA-A- 1225296	11/08/87
		CH-A,B- 662739	30/10/87
		FR-A,B- 2537000	08/06/84
		GB-A,B- 2130916	13/06/84
		JP-C- 1770336	30/06/93
		JP-B- 3016861	06/03/91
		JP-A- 59111736	28/06/84
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		NL-A- 8304089	02/07/84
		SE-B,C- 434214	16/07/84
		SE-A- 8206863	02/06/84
		US-A- 4694832	22/09/87